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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/064,000	04/21/1998	JAMES P. ELIA	796-P-12	5311

7590 09/22/2006

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EXAMINER	
KEMMERER, ELIZABETH	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 09/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/064,000	ELIA, JAMES P.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *382-402* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *382-402* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/21/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The amendment received 26 June 2006 has been entered in full. Claims 1-381 are canceled. Claims 382-402 are under examination.

The second supplemental declarations of Drs. Heuser and Lorincz, submitted under 37 CFR 1.132 with the response, have been entered and will be addressed below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The rejection of claims 382-394 under 35 U.S.C. § 102(b) as being anticipated by Lutjen et al. is *withdrawn* in view of the amended claims reciting a tissue consisting of a desired soft tissue.

35 U.S.C. § 112, Second Paragraph

Claims 383, 384, 391, 393, and 394 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The basis for this rejection is of record, but is repeated herein as per Applicant's request.
Claims 383, 384, and 394 read on methods of administering cells that are "multifactorial and non-specific". It is not clear what is meant by these terms, as the terms are not

used to describe cells in the art. For example, the term "multifactorial" is used to describe causes, effects and processes, not cells. The specification also provides no clear definition. Therefore, the metes and bounds of the claims cannot be determined. Furthermore, new claims 391, 393, and 394 raise similar issues under 35 U.S.C. § 112, second paragraph. Claim 382 recites administration of cells. Claim 391 depends from claim 382 and further recites that the cells comprise pluripotent cells. Claim 393 depends from claim 391 and further recites that the cells are stem cells. Claim 394 depends from claim 393, and further recites that the stem cells are multifactorial and nonspecific. Regarding claims 391 and 393, it is implied that "stem cells" define a narrower sub-genus than "pluripotent cells." However, all pluripotent cells are stem cells. Neither the specification nor the art defines the terms so as to distinguish a difference between "pluripotent cells" and "stem cells." Thus, the metes and bounds of the two claims cannot be determined, and they are indefinite under 35 U.S.C. § 112, second paragraph. Also, claims 383 and 384 imply that "stem cells" defines a narrower sub-genus than "multifactorial and nonspecific cells," whereas claims 393 and 394 imply that "multifactorial and nonspecific cells" defines a narrower sub-genus than "stem cells." The two pairs of claims are contradictory. Since neither the specification nor the art provide a definition of "multifactorial and nonspecific cells," the metes and bounds of the claims cannot be determined, and they are indefinite under 35 U.S.C. § 112, second paragraph.

Applicant's arguments (pp. 6-18, amendment received 26 June 2006) have been fully considered but are not found to be persuasive for the following reasons. e sixth

supplemental information disclosure statement. A signed copy of the 1449 form thereof accompanies this office action.

Applicant argues that the rejection is inconsistent with the decision on a parent patent, 5,759,033. This has been fully considered but is not found to be persuasive. The prior examiner's position is not binding. Furthermore, in general, it is not the policy of the USPTO to perpetuate errors. When issues are first identified, they must be raised.

Applicant refers to Exhibits as additional evidence in support of their position. While these references do, in fact, refer to proteins as multifactorial, they define the exact, specific effects the proteins have. Therefore, the entire phrase "multifactorial and non-specific" as it relates to cells, is still not defined.

Applicant reviews the recent finding in Phillips v. AWH Corporation (75 USPQ2d 1321) that claims are generally given their ordinary and customary meaning in the art, and that claims should be read in the context of the disclosure. Applicant argues that Phillips states that extrinsic evidence is less significant than the intrinsic record. Applicant points to the finding in Phillips that dictionary evidence can be useful, but such evidence is less reliable than specifications and prosecution histories. Applicant argues that the examiner should interpret the words "multifactorial and non-specific" in light of the specification, giving the words their ordinary meaning. Applicant argues that the examiner's interpretation is based on non-contextual sources places the terms out of context and do not enjoy the same weight of evidence as the specification. This has been fully considered but is not found to be persuasive. The examiner takes no issue

with the general principles discussed in Phillips. The specification was the first place consulted by the examiner to breathe life and meaning into the term "multifactorial and non-specific" as applied to cells. As explained previously on the record, neither the specification nor the art provides an unambiguous definition for the term. Page 37 of the specification states, "Multifactorial and nonspecific cells (such as stem cells and germinal cells) can provide the necessary in vivo and in vitro cascade of genetic material once an implanted master control gene's transcription has been activated." The use of "such as" clearly implies that the term "multifactorial and non-specific cells" is intended to encompass cells other than stem cells and germinal cells. However, neither the specification nor the art disclose what these other cells are. In the absence of this information, the skilled artisan cannot determine the metes and bounds of the claims at issue. The functional portion of the definition, "...provide[s] the necessary in vivo and in vitro cascade of genetic material ..." makes no sense. What is a cascade of genetic material? Thus, the specification does not define these terms, and the metes and bounds of the claimed invention cannot be determined. A search of the prior art indicated that the relevant art also does not use the terms "multifactorial and non-specific" in connection with cells. See Appendix A, submitted as evidence, regarding a search done in the database Medline. The first result uses "multifactorial" to describe diseases. The second result uses "multifactorial" to describe a process. The third result uses "multifactorial" to describe a process. The fourth result uses "multifactorial" to describe analyses. The fifth result uses "multifactorial" to describe a process. The sixth result uses "multifactorial" to describe a study. Each of these usages is consistent with

the examiner's position that the term "multifactorial," given its ordinary and customary usage in the art, is used to describe causes, effects and processes, not cells.

Applicant argues that the examiner's position is supported by a lack of search results regarding the terms followed by a series of suppositions and speculations regarding the meaning of the terms. Applicant characterizes the examiner's position as amounting to nothing more than opinion due to lack of evidence. Applicant indicates that one skilled in the medical arts would not interpret "multifactorial" as being limited to processes. Applicant urges that the term "factor" is well known in the medical art, and that "multifactorial" would be understood by one in the medical art to mean more than one factor. This has been fully considered but is not found to be persuasive. The rejection is supported by evidence. See discussion of the specification and attached search results. Finally, Applicant's definition of 'multifactorial" as meaning "more than one factor" makes no sense when applied to cells. What is a "more than one factor cell?"

Applicant refers to the fifth supplemental IDS as providing definitions. Applicant argues that the definitions are confirming evidence that the disputed terms are known and used properly in the specification, and that the IDS identifies the terms as adjectives. This has been fully considered but is not found to be persuasive. Regarding the dictionary definitions provided by the fifth supplemental IDS, the dictionary.net's definition of multifactorial is "involving or depending on several factors or causes (especially pertaining to a condition or disease resulting from the interaction of many genes)." This supports the rejection in that the term "multifactorial" is not used to

describe cells. It is used to describe a cause (for example, of the disease) or an effect (for example, of the genes). Similarly, the dictionary.net's definition of nonspecific is "not caused by a specific agent; used also of staining in making microscope slides; 'nonspecific enteritis'" supports the rejection. "Nonspecific" is not used to describe cells. How can cells be "not caused by a specific agent?" The definition uses the term to describe causes (i.e., nonspecific enteritis is a disease caused by undefined factors). Cells can be in various stages of differentiation. For example, an embryonic stem cell would clearly be completely undifferentiated, as it can differentiate into any cell type. However, a promyelocyte is "undifferentiated" to an extent in that it can differentiate into a basophil, eosinophil, or neutrophil, whereas it cannot differentiate into any other cell type (e.g., keratinocytes, neural cells, muscle cells). The instant specification does not clarify whether such intermediate cells are encompassed by the term "multifactorial and non-specific."

Applicant provides definitions from Merriam Webster's Medline Plus Medical Dictionary, namely:

> Factor: (noun) a substance that functions in or promotes the function of a particular physiological process or bodily system.
> Multifactorial: (adjective) having, involving, or produced by a variety of elements or causes.

Applicant argues that "factor" means a substance such as a cell that promotes a particular physiological process, such as growth of an artery. Applicant argues that "multifactorial" is used to denote the quality of a cell when a variety of elements (factors) promote the growth of an artery. This has been fully considered but is not found to be persuasive. Applicant's definitions support the rejection. Applicant equates "factor" with

"cell." Thus, substituting "cells" for "factors" in Applicant's second sentence, "multifactorial" is used to denote the quality of a cell when a variety of elements [cells] promote the growth of an artery. This simply makes no sense. Regarding the Merriam Webster's Medline Plus Medical Dictionary definition of multifactorial, what types of cells have, involve, or are produced by a variety of elements or causes?

Applicant argues that the terms were understood by those skilled in the art, pointing to the second supplemental declarations of Drs. Heuser and Lorincz. The second supplemental declarations of Drs. Heuser and Lorincz submitted under 37 CFR 1.132 are insufficient to overcome the rejection of claims 383, 384, 391, 393, and 394 based upon 35 U.S.C. § 112, second paragraph because, although the declarations use the term "multifactorial and non-specific cells," they do not explain what cells are encompassed by the term. See section 7 of each of the Heuser and Lorincz second supplemental declarations. In view of the totality of the evidence of record, which includes the specification, prior art of record, and declarations submitted under 37 CFR 1.132, an unambiguous definition of the term "multifactorial and non-specific cells" has not been provided.

Applicant argues that the disclosure of stem cells and germinal cells as two types of multifactorial and non-specific cells, along with pluripotent and bone marrow stem cells, is fully adequate to describe examples of types of cells having the described characteristics. This has been fully considered but is not found to be persuasive. Pluripotent and bone marrow stem cells are stem cells and do not constitute additional species of the genus "multifactorial and non-specific cells." The specification indicates

that multifactorial and non-specific cells include stem cells and germinal cells. What other cells can be encompassed? What definition could resolve the inherent contradiction of the claims wherein claims 383 and 384 imply that stem cells are a subgenus of the genus "multifactorial and non-specific cells" whereas claims 393 and 394 imply that "multifactorial and non-specific cells" are a subgenus of the genus "stem cells?"

Applicant points to Strauer 2005 as stating that the regenerative potential of bone marrow derived stem cells may be explained by any of four mechanisms, and that "mechanisms" are further referred to as "factors." Applicant argues that the cells can be described as four-factor cells, i.e., multifactorial. Applicant concludes that the totality of the evidence indicates that the rejection should be withdrawn. Applicant also argues that "non-specific" is synonymous with "non-specialized." This has been fully considered but is not found to be persuasive. Strauer 2005 uses "four mechanisms" to describe "regenerative potential," not the cells *per se*. Even if Strauer 2005 could be tortuously construed as describing bone marrow stem cells as multifactorial, Strauer 2005 only discusses bone marrow stem cells. The specification already indicates that stem cells are exemplary of "multifactorial and non-specific" cells. The issue is what cells other than stem cells and germinal cells can be considered multifactorial and non-specific, given that the art does not apply these terms to cells.

Applicant takes issue with the examiner's characterization of Strauer 2005, stating that Strauer 2005 supports the specification's definition that bone marrow stem cells are a type of multifactorial and non-specific cells. This has been fully considered

but is not found to be persuasive. Strauer 2005 does not use the phrase "multifactorial and non-specific" to describe cells. Strauer 2005 uses "four mechanisms" to describe "regenerative potential" and not cells *per se,* thus supporting the rejection.

Applicant points to Caplan 1991 and Caplan 2001 as using the term "multifactorial" to describe cells. Regarding Caplan 1991, the examiner is at a loss as to how Applicant can conclude that the publication uses the term "multifactorial and non-specific" to describe MSCs from the quoted passages. Caplan 2001 uses the term "multifactorial" to describe the differentiation pathway, a process, and thus supports the examiner's position.

Applicant refers to Exhibits F (Merck Manual) and G (NIH publication). These publications have been fully considered but are not found to support Applicant's position. Exhibit F uses the term "multifactorial" to describe a protein. Exhibit G describes a drug as a non-specific growth factor for megakaryocytes. Neither resolves the issue since it does not address the question of what "mutlifactorial and non-specific" means in terms of cells.

Applicant concludes by stating that the examiner is apparently the only person who does not understand the term "multifactorial and non-specific" as it applies to cells. This has been fully considered but is not found to be persuasive, since the rejection is based upon painstaking consideration of the specification and extrinsic evidence. In view of the preponderance of the totality of the evidence, the rejection is maintained.

Regarding the contradiction of claims 383 to 384 compared to claims 393 and 394, Applicant provides a confusing discussion that does not clarify the issue. Is

Applicant implying that not all stem cells are multifactorial and non-specific? If so, the indefiniteness of the phrase as applied to cells is compounded.

New Rejections/Objections, Necessitated by Amendment

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 382 (and dependent claims 383-402) are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. Independent claim 382 has been amended to recite a "method for producing and integrating tissue consisting of a desired soft tissue" comprising administering cells. The specification as originally filed does not appear to have support for formation of one tissue to the exclusion of others by administration of cells. The amendment of 26 June 2006 did not point to specific portions of the specification as originally filed for support of such claim language.

Claim Objections

Claims 385-388, 390, and 392 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 385-388, 390, and 392 depend from independent claim 382 which now recites closed claim language with respect to the type of tissue to be formed. Claim 382 now appears to be limited to the formation of a single soft tissue type, rather than soft tissue comprising several different tissue types. However, dependent claims 385-388, 390, and 392 recite formation of additional tissues, or soft tissues *comprising* a particular type of tissue (implying the potential existence of other types). Therefore, the dependent claims appear to improperly expand the subject matter of the claim from which they depend.

It is noted that claims 385-388, 390, and 392 were not rejected under 35 U.S.C. § 102(b) as being anticipated by Lutjen et al. because they depend from claim 382 which has defined around Lutjen et al. Applicant is put on notice that amending claims 385-388, 390, and/or 392 so that they are independent may cause reinstatement of the rejection over Lutjen et al.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful; the examiner's supervisor, Gary Nickol, Ph.D. can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Elizabeth C. Kemmerer

ECK

ELIZABETH KEMMERER
PRIMARY EXAMINER

APPENDIX

Dialog level 05.10.03D
Logon file001 14feb06 16:17:11
*File 155: Medline has resumed updating.

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    Set  Items  Description
    ---  -----  ----------
? s (multifactorial (2N) cell?) and stem
        12971  MULTIFACTORIAL
      2761033  CELL?
           66  MULTIFACTORIAL(2N)CELL?
       143636  STEM
    S1      6  (MULTIFACTORIAL (2N) CELL?) AND STEM
? t s1/7/1-6

 1/7/1
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2006 Dialog. All rts. reserv.
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18357667 PMID: 16020348
Current concepts in ocular surface reconstruction.
Dogru Murat; Tsubota Kazuo
Tokyo Dental College, Chiba, Japan.
Seminars in ophthalmology (United States) Apr-Jun 2005, 20 (2) p75-93, ISSN 0882-0538 Journal Code: 8610759
Publishing Model Print
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Diseases that affect the limbal %%%stem%%% %%%cells%%% are %%%multifactorial%%% and present with different stages of severity. The most important features to be considered in evaluating these patients include the degree of limbal %%%stem%%% cell loss, the extent of conjunctival disease, and the presence and etiology of ocular surface inflammation. Other important factors are tear film and eyelid abnormalities, keratinization of the ocular surface, laterality of the disease process, health and age of the patient. Careful consideration of all of these factors help tremendously in tailoring the most suitable method of treatment for each patient. The management of severe ocular surface disease has benefited from numerous advances in recent years. At one time, available techniques for visual rehabilitation consisted of superficial keratectomy, use of artificial tears, tarsorraphy as well as lamellar and penetrating keratoplasty. A lamellar or penetrating keratoplasty procedure resulted in a stable surface only for as long as the donor epithelium was present and once the epithelium sloughed off, the ocular surface failed due to conjunctivalization. The last few decades enjoyed the development and, especially, progress of new ocular surface reconstruction techniques such as amniotic membrane transplantation, limbal %%%stem%%% cell transplant procedures, transplantation of cultivated oral mucosal or limbal %%%stem%%% cell sheets. This review will briefly focus on the indications and methodology of each procedure and the currently available clinical data on the results of these procedures. (66 Refs.)

Record Date Created: 20050715
Record Date Completed: 20050818

1/7/2
DIALOG(R)File 155:MEDLINE(R)

15341984 PMID: 15145210
Robust conversion of marrow cells to skeletal muscle with formation of marrow-derived muscle %%%cell%%% colonies: a %%%multifactorial%%% process.
Abedi Mehrdad; Greer Deborah A; Colvin Gerald A; Demers Delia A; Dooner Mark S; Harpel Jasha A; Weier Heinz-Ulrich; Lambert Jean-Francois; Quesenberry P J
Roger Williams Medical Center, Department of Research, Providence, RI 02864, USA. mabedi@rwmc.org
Experimental hematology (Netherlands) May 2004, 32 (5) p426-34, ISSN 0301-472X Journal Code: 0402313
Contract/Grant No.: 1P22-RR-18757-01; RR; NCRR; P01-DK-5022; DK; NIDDK; P01-HL-56920; HL; NHLBI; R01-DK-2742; DK; NIDDK; R01-DK-49650; DK; NIDDK
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
OBJECTIVE: Murine marrow cells are capable of repopulating skeletal muscle fibers. A point of concern has been the "robustness" of such conversions. We have investigated the impact of type of cell delivery, muscle injury, nature of delivered cell, and %%%stem%%% cell mobilizations on marrow-to-muscle conversion. METHODS: We transplanted green fluorescence protein (GFP)-transgenic marrow into irradiated C57BL/6 mice and then injured anterior tibialis muscle by cardiotoxin. One month after injury, sections were analyzed by standard and deconvolutional microscopy for expression of muscle and hematopoietic markers. RESULTS: Irradiation was essential to conversion, although whether by injury or induction of chimerism is not clear. Cardiotoxin- and, to a lesser extent, PBS-injected muscles showed significant number of GFP(+) muscle fibers, while uninjected muscles showed only rare GFP(+) cells. Marrow conversion to muscle was increased by two cycles of G-CSF mobilization and to a lesser extent by G-CSF and steel or GM-CSF. Transplantation of female GFP to male C57BL/6 and GFP to ROSA26 mice showed fusion of donor cells to recipient muscle. High numbers of donor-derived muscle colonies and up to 12% GFP(+) muscle cells were seen after mobilization or direct injection. These levels of donor muscle chimerism approach levels that could be clinically significant in developing strategies for the treatment of muscular dystrophies. CONCLUSION: In summary, the conversion of marrow to skeletal muscle cells is based on cell fusion and is critically dependent on injury. This conversion is also numerically significant and increases with mobilization.
Record Date Created: 20040517
Record Date Completed: 20040624

1/7/3
DIALOG(R)File 155:MEDLINE(R)

13036731 PMID: 11000981
Mobilization of peripheral blood progenitor cells for autografting: chemotherapy and G-CSF or GM-CSF.
Siena S; Bregni M; Gianni A M

The Falck Division of Medical Oncology, Ospedale Niguarda, Cai Granda, Milan, Italy.
Bailliere's best practice & research. Clinical haematology (ENGLAND) Mar-Jun 1999, 12 (1-2) p27-39, ISSN 1521-6926 Journal Code: 100900679
Publishing Model Print
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The mobilization of haematopoietic progenitor %%%cells%%% is a %%%multifactorial%%% process, still poorly understood at the molecular level. Mobilized haematopoietic progenitors, as defined by the expression of CD34 cell surface molecule, comprise heterogeneous subpopulations of cells committed to different haematopoietic lineages. Haematopoietic progenitors may be mobilized by chemotherapy alone, haematopoietic growth factors alone, or by chemotherapy plus haematopoietic growth factors. The choice of a mobilization regimen that allows an optimal yield of progenitors with a minimum number of leukaphereses should incorporate, in most patients, a disease-specific chemotherapeutic agent(s) plus a haematopoietic growth factor, to be continued until completion of harvest. (76 Refs.)
Record Date Created: 20001019
Record Date Completed: 20001019

1/7/4
DIALOG(R)File 155:MEDLINE(R)

12278080 PMID: 9588003
Advances in hematopoietic %%%stem%%% cell culture.
Audet J; Zandstra P W; Eaves C J; Piret J M
Biotechnology Laboratory, University of British Columbia, Vancouver, Canada.
Current opinion in biotechnology (ENGLAND) Apr 1998, 9 (2) p146-51, ISSN 0958-1669 Journal Code: 9100492
Publishing Model Print
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Recent advances in our understanding of the earliest stages of hematopoietic cell differentiation, and how these may be manipulated under defined conditions in vitro, have set the stage for the development of robust bioprocess technology applicable to hematopoietic cells. Sensitive and specific assays now exist for measuring the frequency of hematopoietic %%%stem%%% cells with long-term in vivo repopulating activity from human as well as murine sources. The production of natural or engineered ligands through recombinant DNA and/or combinatorial chemistry strategies is providing new reagents for enhancing the productivity of hematopoietic %%%cell%%% cultures. %%%Multifactorial%%% and dose-response analyses have yielded new insight into the different types and concentrations of factors required to optimize the rate and the extent of amplification of specific subpopulations of primitive hematopoietic cells. In addition, the rate of cytokine depletion from the medium has also been found to be dependent on the types of cell present. The discovery of these cell-type-specific

parameters affecting cytokine concentrations and responses has introduced a new level of complexity into the design of optimized hematopoietic bioprocess systems. (49 Refs.)
Record Date Created: 19980608
Record Date Completed: 19980608

1/7/5
DIALOG(R)File 155:MEDLINE(R)

11563022 PMID: 8875201
Role of the basal cells in premalignant changes of the human prostate: a %%%stem%%% cell concept for the development of prostate cancer.
Bonkhoff H
Institute of Pathology, University of the Saarland, Homburg/Saar, Germany.
European urology (SWITZERLAND) 1996, 30 (2) p201-5, ISSN 0302-2838
Journal Code: 7512719
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
OBJECTIVES: Prostatic intraepithelial neoplasias (PIN) result from abnormal differentiation and proliferation processes within the prostatic epithelial cell system. Recent data indicate that basal cells are essentially involved in normal and abnormal growth patterns of the human prostate. RESULTS: The basal cell layer represents the proliferative compartment and most probably houses the prostatic %%%stem%%% cell population. Basal cells are targets of several regulatory factors including estrogens, androgens, epidermal growth factor and other nonsteroidal growth factors. During the malignant transformation of the prostatic epithelium (PIN), the basal cell layer loses its proliferative function which is transferred to secretory luminal cell types. These proliferative abnormalities are attended by severe regulatory disorders of the programmed cell death within the prostatic epithelial cell system. The Bcl-2 oncoprotein which blocks the programmed cell death in the proliferative compartment (basal cell layer) in normal conditions, extends to the secretory luminal cell types in high-grade PIN lesions. This, in turn, may increase the genetic instability of the dysplastic epithelium. During the process of tumor invasion, the transformed cells lose their basal cell-specific phenotype and acquire features of exocrine cell types which represent the major phenotype in common prostate cancer. At the point of stromal invasion, the transformed cells produce neoplastic basement membrane material which allows them to penetrate the extracellular matrix. CONCLUSION: These data provide theoretical bases for a %%%stem%%% cell concept in the development of prostate cancer and highlights the importance of basal %%%cells%%% in this %%%multifactorial%%% process.
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[T-cell-rich B-%%%cell%%% lymphoma: %%%multifactorial%%% study of 4 cases]

Linfoma B rico en celulas T: estudioo multifactorial de cuatro casos.

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PURPOSE: With the correlational study of four cases in several areas (clinic, morphoimmunologycal, ultrastructural and genetic) we try to valorate the still controversial entity known as T-cell rich B-cell lymphoma (TRBL), and stablish some useful clues in order to settle down the differential diagnosis between TRBL, Hodgkin's disease (HD), and T-cell non-Hodgkin's lymphomas (TNHL). PATIENTS AND METHODS: Cases proceeded from Oncology Department, and had been firstly misdiagnosed either as HD (3 cases) or as TNHL (1 case). Biopsies were processed and stained in routine way, H&E, Giemsa and Wilder. Immunohystological study, using monoclonal antibodies against B-cells, T-cells, histiocytes, activation and proliferation markers, was also performed with avidin biotine peroxidase (ABC) method. Ultrastructural study was performed in three of the cases; two patients were studied by PCR and Southern blot. RESULTS: All of the cases showed a diffuse hystological pattern, with variable fibrosis, and proliferation of venules and capillaries. Small lymphoid cells, being positive for CD3, were dominant. Large blastic cells, positive for CD20, some of them with a Sternberg-like appearance, could be found, in a spitty pattern. Histiocytes were abundant and positive to CD68. Proliferation index (Ki-67) ranged between 13 and 24.5% being the stain mainly positive for B-cells and in a certain extent, also for T-cells. Ultrastructural features were closer to those of the NHL than to the ones found in HD. Molecular study failed to prove any rearrangement. CONCLUSIONS: TRBL is a rare entity between B-cell NHL group. Diagnosis and differential diagnosis (mostly with HD and T-cell NHL) have to be properly made, because of the very distinct prognosis and therapy.

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